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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,095	09/18/2003	Robert P. Hammer	Hammer 0212.1	6953

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PATENT DEPARTMENT
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EXAMINER	
RUSSEL, JEFFREY E	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 07/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/666,095	HAMMER ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8 and 19-52* is/are rejected.

7)☒ Claim(s) *4 and 9-18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20030918*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The election of species requirement and restriction requirement set forth in the Office action mailed April 1, 2005 are withdrawn. Claims 1-52 have been examined on their merits.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reasons:

SEQ ID NO:4 as defined in the Sequence Listing filed September 18, 2003 does not correspond to those sequences identified as SEQ ID NO:4 in the specification and claims. Note that the C-terminal residues in the sequence listing are Leucine residues, whereas the C-terminal residues in the specification and claims are lysine residues. It is believed that the latter is correct, in view of the definition of S as being a hydrophilic region, and that the sequence listing needs correction.

Applicant must provide a substitute computer readable form (CRF) copy of the Sequence Listing, a substitute paper copy of the Sequence Listing as well as an amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and include no new matter as required by 37 CFR 1.825(a) and (b).

The Sequence Listing filed September 18, 2003 was approved by STIC for matters of form.

3. The abstract of the disclosure is missing from the image file wrapper for this application. Note that the Abstract which was printed in the corresponding U.S. Patent Application Publication was actually a portion of the abstract from one of the prior art documents cited in the

Information Disclosure Statement filed September 18, 2003, namely from the Fu PhD Dissertation. Applicants are requested to re-submit the abstract of the disclosure.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150 (CCPA 1977) and have been adopted by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. With respect to (1), the nature of the invention is the prevention or treatment of diseases involving toxic amyloid proteins or peptides, such as Alzheimer's disease. With respect to (2), only one prior art reference (Soto-Jara - U.S. Patent No. 6,689,753) has been located which uses a peptide comprising disubstituted amino acids to treat the same diseases treated by Applicants. This prior art peptide, while encompassed by Applicants' generic structural formulas, is patentably distinct from Applicants' specific compounds. Further, Applicants' specification cautions against using

the disubstituted amino acid, Aib, used by the reference. See page 12, lines 22-26. As characterized by the Conway et al article (Current Pharm. Des., Vol. 9, pages 427-447), "the development of disease modifying therapies based on the amyloid hypothesis is still in its infancy". See page 439, column 1, last paragraph. The Conway et al article also teaches away from the use of peptides as therapeutic agents due to their poor oral bioavailability and susceptibility to proteolysis. See page 433, column 2, last paragraph. With respect to (3), the relative skill of those in the art is high. With respect to (4), the art, like all pharmaceutical arts, is relatively unpredictable. Further, as noted by the Conway et al article (page 427, paragraph bridging columns 1 and 2), there is no clear etiology for Alzheimer's disease, and even diagnosis is difficult, which significantly undercuts the ability of the artisan to predict the outcome of experimentation. With respect to (5), the claims embrace the use of a vast number of peptides (having four or more amino acids) for the treatment of any or all diseases involving toxic amyloid proteins or peptides. The peptides are not structurally limited, except that at least one amino acid must be $C^{\alpha,\alpha}$-disubstituted, again with no limitations on the disubstitutions. With respect to (6), Table 1 of the specification lists 21 amyloid-based diseases, and Table 2 lists nine aggregation-inducing sequences that may be responsible for amyloid toxicity. However, only four specific active agents are disclosed in the specification, which are all related to the aggregation-inducing sequence KLVFFA which is specific to Alzheimer's disease. With respect to (7), there are no working examples present in the specification. There are two in vitro tests of two specific active agents, one involving dissolution of fibrils from a mica surface (see page 23, paragraph [0065]), the other involving an unspecified solution aggregation test (see page 25, paragraph [0072]). The tests do not involve the transgenic mouse models of Alzheimer's disease

discussed at paragraph [0067]. Further, the in vitro tests which are reported in Applicants' specification do not address an aspect of unpredictability pointed out by the Conway et al article at page 439, column 2, last paragraph, namely that aggregation modulation therapies may actually accelerate disease progression by increasing the population of toxic non-fibrillar oligomeric Aβ. With respect to (8), the quantity of experimentation necessary to practice the invention would be vast, given the breadth of the peptides to be used, the breadth of the diseases to be treated, and the relative lack of specific peptides and working examples in the specification. The Fu dissertation (Louisiana State University, December 2002), after discussing an anti-aggregation study involving AMY-1/SEQ ID NO:4, states that the "study offers the promise of understanding the inhibition mechanism of anti-fibrillogenesis with β-strand mimics and may facilitate the development of novel inhibitors which prevent amyloidogenesis in vivo in Alzheimer's disease." This is indicative of the need of significant amounts of further research in order to practice the invention. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

5. Claims 3 and 24 are deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/412,081 because the provisional application, under the test of 35 U.S.C. 112, first paragraph, discloses the claimed invention.

Instant claims 1, 2, 4-23, and 25-52 are not deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/412,081 because the provisional application, under the test of 35 U.S.C. 112, first paragraph, does not disclose all of the generic formulas recited in instant claims 1 and 51; does not disclose compounds corresponding to SEQ ID NOS:5, 6, and 7; does not disclose aggregation-inducing sequences corresponding to SEQ ID

NOS:9-16 or Q_m where m is an integer from 25 to 45; and does not disclose combining the compounds with a pharmaceutically acceptable carrier in general. Note that unless a claim is limited exclusively to subject matter disclosed in a priority application, the claim is not entitled to the benefit of the filing date of the priority application. See MPEP 201.11(I) and (VI).

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1, 2, 7, 8, 19, 20, 51, and 52 are rejected under 35 U.S.C. 102(b) and claim 3 is rejected under 35 U.S.C. 102(a) as being anticipated by the Fu et al article (Organic Letters, Volume 4, pages 237-240, published on Web 12/22/2001). The Fu et al article teaches Applicants' elected peptide, Lys-Digb-Val-Dbzg-Phe-Dpg-$(Lys)_6$-NH_2. See page 239, column 1.

8. Claims 1, 19, and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by the Fu et al article (J. Org. Chem., Vol. 66, pages 7118-7124). The Fu et al article teaches the peptide Lys-Dbg-Ala-Dpg-Glu-NH_2. See Figure 3A. The peptide of the Fu et al article corresponds to the first peptidyl sequence of claim 1 wherein X_{aa1} is Lys, Y_{AA1} is Dbg, X_{aa2} is Ala, Y_{AA2} is Dpg, S is Glu, and n=1. The peptide also corresponds to the second peptidyl sequence of claim 1 wherein n=0, X_{aa1} is Lys, Y_{AA1} is Dbg, X_{aa2} is Ala, Y_{AA2} is Dpg, and the C-terminal end

comprises an additional functionality (i.e. Glu) that does not adversely affect the compound's ability to inhibit the toxicity of an amyloid protein or amyloid peptide as compared to an otherwise identical compound lacking such additional functionality. The peptide also corresponds to the third peptidyl sequence of claim 1 wherein Y_{AA1} is Dbg, X_{aa1} is Ala, Y_{AA2} is Dpg, X_{aa2} is Glu, n=0, and the N-terminal end comprises an additional functionality (i.e. Lys) that does not adversely affect the compound's ability to inhibit the toxicity of an amyloid protein or amyloid peptide as compared to an otherwise identical compound lacking such additional functionality. The peptide also corresponds to the fourth peptidyl sequence of claim 1 wherein S is Lys, n=1, Y_{AA1} is Dbg, X_{aa1} is Ala, Y_{AA2} is Dpg, and X_{aa2} is Glu. The peptide also corresponds to the fifth and sixth peptidyl sequences of claim 1 wherein X_{aa1} is Lys, Y_{AA1} is Dbg, X_{aa2} is Ala, Y_{AA2} is Dpg, X_{aa3} is Glu, and n=0. In view of the similarity in structure between the peptide of the Fu et al article and Applicants' claimed peptidyl sequences, the peptide of the Fu et al article inherently will be capable of inhibiting the toxicity of an amyloid protein or amyloid peptide to the same extent claimed by Applicants. Sufficient evidence of similarity is deemed to be present the peptide of the Fu et al article and Applicants' claimed compounds to shift the burden to Applicants to provide evidence that the claimed compounds are unobviously different than the peptide of the Fu et al article. Note that patentability is not imparted to product claims merely upon the employment of descriptive language not chosen by the prior art. In re Skoner, 186 USPQ 80, 82 (CCPA 1975). The discovery of a new property or use for a previously known compound can not impart patentability to claims drawn to the compound. In re Schoenwald, 22 USPQ2d 1671 (CAFC 1992).

9. Claims 1-3, 6-8, 19-21, 51, and 52 are rejected under 35 U.S.C. 102(a) as being anticipated by the Fu dissertation (Louisiana State University, December 2002). The Fu dissertation teaches peptides at page 24, Table 2.1, and at page 123, Table 5.1, and at page 126, peptides AMY-3 and AMY-4, which comprise the same peptidyl sequences recited in instant claim 1. For example, DPG-4 of the Fu dissertation corresponds to the ninth peptidyl sequence of claim 1 wherein X_{aa1} is Lys, Y_{AA1} is Dbg, X_{aa2} is Val, Y_{AA2} is Dpg, and X_{aa3} is Thr, Y_{AA3} is Dpg, n=0, and the C-terminal end comprises an additional functionality (i.e. Val-Dpg-Glu) that does not adversely affect the compound's ability to inhibit the toxicity of an amyloid protein or amyloid peptide as compared to an otherwise identical compound lacking such additional functionality. Alternatively, DPG-4 corresponds to the ninth peptidyl sequence of claim 1 wherein X_{aa1} is Val, Y_{AA1} is Dbg, X_{aa2} is Thr, Y_{AA2} is Dpg, and X_{aa3} is Val, Y_{AA3} is Dpg, S is Gly, n=1, and the N-terminal end comprises an additional functionality (i.e. Lys-Dpg) that does not adversely affect the compound's ability to inhibit the toxicity of an amyloid protein or amyloid peptide as compared to an otherwise identical compound lacking such additional functionality. The peptides of Table 2.1 of the Fu dissertation are combined in phosphate-buffered aqueous solution (see page 30), which corresponds to the pharmaceutically acceptable carrier of instant claim 21. In view of the similarity in structure between the peptides of the Fu dissertation and Applicants' claimed peptidyl sequences, the peptides of the dissertation inherently will be capable of inhibiting the toxicity of an amyloid protein or amyloid peptide to the same extent claimed by Applicants. Sufficient evidence of similarity is deemed to be present the peptides of the Fu dissertation and Applicants' claimed compounds to shift the burden to Applicants to provide evidence that the claimed compounds are unobviously different than the

peptides of the Fu dissertation. Note that patentability is not imparted to product claims merely upon the employment of descriptive language not chosen by the prior art. In re Skoner, 186 USPQ 80, 82 (CCPA 1975). The discovery of a new property or use for a previously known compound can not impart patentability to claims drawn to the compound. In re Schoenwald, 22 USPQ2d 1671 (CAFC 1992). The Fu dissertation also teaches the peptide AMY-1, which corresponds to Applicants' elected SEQ ID NO:4 and which is combined with a phosphate-buffered aqueous solution, and the peptide AMY-2, which corresponds to Applicants' SEQ ID NO:7. See pages 103, 108, and 126.

10. Claims 1-3, 5, 7, 8, 19-21, 51, and 52 are rejected under 35 U.S.C. 102(a) as being anticipated by the Aucoin oral presentation, "Dissection of an Amyloid Aggregation Inhibitor", 225th American Chemical Society conference, New Orleans, LA, March 23-27, 2003. The Aucoin oral presentation, as evidenced by the presentation notes supplied in the Information Disclosure Statement filed September 18, 2003, disclosed peptides AMY-1 and AMY-3 which correspond to Applicants' claimed compounds of SEQ ID NOS:4 and 6, respectively. The peptides are combined with a phosphate-buffered aqueous solution, which corresponds to Applicants' pharmaceutically acceptable carrier.

The Aucoin oral presentation satisfies the requirement of 35 U.S.C. 102(a) that an invention be "known... by others in this country" because the identity of the presenter is different than the inventorship of the instant application, and any difference in authorship/inventorship satisfies the statutory requirement of "by another". See MPEP 2132(III). See also Ecolochem Inc. v. Southern California Edison, 56 USPQ2d 1065, 1071 (CAFC 2002), where the court acknowledges that oral presentations can satisfy the requirements of 35 U.S.C.

102(a). This rejection could be overcome, e.g., by the submission of a declaration under 37 CFR 1.132 showing that the subject matter of the presentation was derived from the instant inventors and was therefore not "by another". See MPEP 715.01(c), 716.10, and 2136.05.

Note that the Aucoin oral presentation is not considered to be a printed publication because insufficient evidence is of record as to whether printed copies, slides, etc. of oral presentation were made available and/or whether members of the public had time to make copies of the disclosed subject matter. Compare In re Klopfenstein, 72 USPQ2d 1117 (CAFC 2004).

11. Claims 1, 7, 8, 21, 22, 28, 29, 42-50, and 52 are rejected under 35 U.S.C. 102(e) as being anticipated by Soto-Jara (U.S. Patent No. 6,689,753). Soto-Jara teaches the peptide Leu-Aib-Phe-Phe-Asp which inhibit β-pleated sheet formation in amyloid-β peptides and is used to treat Alzheimer's disease. The peptide can be combined with pharmaceutically acceptable carriers. See, e.g., the Abstract and claims 1, 7, and 23. The peptide of Soto-Jara corresponds to the first peptidyl sequence of claim 1 wherein X_{aa1} is Leu, Y_{AA1} is Aib, X_{aa2} is Phe, Y_{AA2} is Phe, S is Asp, and n=1. The peptide also corresponds to the second peptidyl sequence of claim 1 wherein n=0, X_{aa1} is Leu, Y_{AA1} is Aib, X_{aa2} is Phe, Y_{AA2} is Phe, and the C-terminal end comprises an additional functionality (i.e. Asp) that does not adversely affect the compound's ability to inhibit the toxicity of an amyloid protein or amyloid peptide as compared to an otherwise identical compound lacking such additional functionality. The peptide also corresponds to the third peptidyl sequence of claim 1 wherein Y_{AA1} is Aib, X_{aa1} is Phe, Y_{AA2} is Phe, X_{aa2} is Asp, n=0, and the N-terminal end comprises an additional functionality (i.e. Leu) that does not adversely affect the compound's ability to inhibit the toxicity of an amyloid protein or amyloid peptide as compared to an otherwise identical compound lacking such additional functionality. The peptide

also corresponds to the fourth peptidyl sequence of claim 1 wherein S is Leu, n=1, Y_{AA1} is Aib, X_{aa1} is Phe, Y_{AA2} is Phe, and X_{aa2} is Asp. The peptide also corresponds to the fifth and sixth peptidyl sequences of claim 1 wherein X_{aa1} is Leu, Y_{AA1} is Aib, X_{aa2} is Phe, Y_{AA2} is Phe, X_{aa3} is Asp, and n=0. In view of the similarity in structure, function, and use between the peptide of Soto-Jara and Applicants' claimed peptidyl sequences, the peptide of Soto-Jara inherently will be capable of inhibiting the toxicity of an amyloid protein or amyloid peptide comprising the aggregation-inducing sequences of claims 7 and 8 to the same extent claimed by Applicants. Because the same active agent is being administered to the same patients according to the same method steps, inherently the peptides of Soto-Jara will promote aggregation of an amyloid protein or amyloid peptide into a non-toxic, non-fibril conformation, will cause a reduction in concentration of protofibrils from an amyloid protein or amyloid peptides, will cause dissolution of fibrils of the amyloid protein or amyloid peptide, and will inhibit Parkinson's disease and Type II diabetes to the same extent claimed by Applicants. Sufficient evidence of similarity is deemed to be present the peptide and method of Soto-Jara and Applicants' claimed compounds and methods to shift the burden to Applicants to provide evidence that the claimed compounds and methods are unobviously different than the peptide and method of Soto-Jara. Note that patentability is not imparted to product claims merely upon the employment of descriptive language not chosen by the prior art. In re Skoner, 186 USPQ 80, 82 (CCPA 1975). The discovery of a new property or use for a previously known compound can not impart patentability to claims drawn to the compound. In re Schoenwald, 22 USPQ2d 1671 (CAFC 1992).

12. Claims 4 and 9-18 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The prior art of record does not teach or suggest compounds having the structures recited in these claims.

The LeVine article (Curr. Med. Chem., Vol. 9, pages 1121-1133) is cited to show the general state of the art.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Bruce Campell can be reached at (571) 272-0974. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.

Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

July 20, 2005